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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/964,412
Filing Date: September 28, 2001
Appellant(s): DE LA MONTE ET AL.

Frank Cottingham
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 3/01/05 appealing from the Office action mailed 6/01/04.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

Appellant has listed related Appeals at page 4 of the Brief filed 3/01/05. The examiner notes that application No. 09/964,667 now has an Appeal Brief filed 4/22/05.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

It is noted that applicant has noted that no Advisory action was received from the office. It is noted that there was some confusion as to the status of the application. The "Final Office Action" applicant refers to as mailed 6/01/04 was counted and processed as a non-final action by the office. It is noted, however that the body of the action stated that it was final while the Form 326 indicated that the action was non-final. The claims have either been rejected twice or have been finally rejected and the filing of the Brief is timely. The examiner contacted appellants representative on 5/11/05 to discuss the

status of the application and it was agreed to continue in the Appeal process. The amendments filed 5/27/04 have been entered into the application.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

The following is a listing of the evidence (e.g., patents, publications, Official Notice, and admitted prior art) relied upon in the rejection of claims under appeal.

Agrawal, S., TIBTECH, Vol. 14:376-387, October 1996.

Branch, A., TIBS Vol. 23, February 1998.

Jen et al., STEM CELLS Vol. 18:307-319, 2000.

Galderisi et al., J. Cell. Physiol. Vol. 181:251-257, 1999.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35 and 37-42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is drawn to the treatment or prevention of dementias of Alzheimer's type of neuronal degeneration via the administration of antisense based nucleic acid based compounds. The antisense oligonucleotides correspond to a sequence of NTP mRNA defined by nucleotides 150-1139 of SEQ ID NO: 1.

The instant specification as filed provides only general guidance for antisense based drugs in treating disease. The specification provides general methodologies for determining effective sequences for the nucleic acid compounds used in the method and provides general methods for delivery of compounds in a treatment, for example (see pages 24-33). Example 8 of the specification shows that the recombinant over-expression of AD7c-NTP in cells in culture produces phenotypes associated with Alzheimer's disease neurodegeneration (see page 46, for example). It is noted, and quite important for one in the art to develop an antisense drug, that it is not clear what

particular AD7c-NTP was used in the example since "AD7c-NTP" is defined by the instant specification to include variants (see page 17, for example).

The instant specification does not provide any specific guidance such as what particular antisense can be used effectively in the claimed method. The practitioner is left to perform trial and error experimentation to find antisense that may be an effective inhibitor that might be used in a method of treatment. The instant specification does not provide guidance or examples that would show by correlation what sequences of antisense based nucleic acid compounds of the method would predictably provide for treatment of disease in general or for the treatment of dementias of Alzheimer's type of neuronal degeneration specifically. The instant specification does not provide guidance or examples that would show by correlation what modes of delivery would predictably provide for a treatment of disease in general and for the treatment of dementias of Alzheimer's type of neuronal degeneration in particular. The specification, as asserted above, provides general methodologies but no specific guidance for one in the treatment of dementia in Alzheimer's type of neuronal degeneration. It is not taught, for example, how or when one in the art must begin a treatment regime in order to prevent dementia. How does one maintain antisense in target cells at a level, and at what level and for how long, such that dementia is prevented? The specification essentially presents many possible general methodologies but fails to indicate how any particular methodology would be appropriate for the specific disease to be treated. The specification does not, for example, provide guidance on how to deliver antisense to neuronal cells but asserts that one in the art only has to use/find/determine by trail and

error experimentation, a means of delivery that will. This amounts to an invitation to find an appropriate method of delivery such that a treatment might be obtained. Would one in the art accept that a subcutaneous injection or transdermal administration would provide antisense to the brain such that dementia would be prevented? The instant specification does not provide any examples of inhibiting AD7c-NTP in cells in culture or in an animal or provide guidance that would show by correlation the treatment or prevention of dementias of Alzheimer's type of neuronal degeneration via the administration of antisense based nucleic acid compounds. The specification provides a system that may screen for compounds that may inhibit AD7c-NTP, but the specification has failed to provide one in the art a means to predictably make a nucleic acid based compound used in the claimed method of treatment or prevention such that no undue experimentation would be required in the making of the compound (ie selection of a predictable effective [in vivo] sequence) and further how to deliver such a compound in a whole animal such that one would be able to treat dementias of Alzheimer's type of neuronal degeneration without undue trial and error experimentation.

The art of nucleic acid based therapies in an unpredictable art. Agrawal [TIBTECH, Vol. 14:376-387, October 1996] states the following: " [t]here are two crucial parameters in drug design: the first is the identification of an appropriate target in the disease process, and the second is finding an appropriate molecule that has specific recognition and affinity for the target, thereby interfering the disease process" (page376); "[o]ligonucleotide must be taken up by cells in order to be effective. [s]everal reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell

lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides {The instant specification fails to provide any guidance or examples that show an uptake of nucleic acid compound that would correlate to a predictable treatment of dementias of Alzheimer's type of neuronal degeneration , for example}. Cellular uptake of oligonucleotides is a complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum . . .[i]t is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency." (Page 378); "[m]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page379); "[a]ny antisense activity observed in such artificial systems [cell culture] should be scrutinized carefully with respect to the disease process and its applicability to *in vivo* situations." (Page 379). The instant specification fails to consider the problems asserted above, for example. The specification fails to provide any particular guidance on how to deliver adequate oligonucleotides to a specified target cell such that there is a treatment of dementias of Alzheimer's type of neuronal degeneration.

Branch [TIBS Vol. 23, February 1998] addresses the unpredictability and the problems faced in the antisense art with the following statements: "[a]ntisense molecules and ribozymes capture the imagination with their promise or rational drug design and exquisite specificity. [h]owever, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "[t]o minimize unwanted non-antisense effects, investigators are

searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. [t]his is a challenging quest."; "[h]owever, their unpredictability confounds research applications of nucleic acid reagents."; "[n]on-antisense effects are not the only impediments to rational antisense drug design. [t]he internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,. . ."; "Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters."; "because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. [a]ntisense compounds are no exception. [a]s is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve and therapeutic index is known."; [c]ompared to the dose response curves of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "[b]ecause it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "[b]inding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. [s]ince accessibility cannot be predicted, rational design of antisense molecules is not possible."; and, "[t]he relationship between accessibility to

ODN binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored. . . [i]t is not yet clear whether *in vitro* screening techniques. . . will identify ODNs that are effective *in vivo*."

Jen et al [STEM CELLS Vol. 18:307-319, 2000] discuss antisense based therapy and the challenges that remain before the use of antisense becomes routine in a therapeutic setting. Jen et al discuss the advances made in the art but also indicate that progress needs to be made in the art. In the conclusion of their review Jen et al assert "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also stated "[t]he key challenges to this field have been outlined above. [I]t is clear that they will have to be solved if this approach to specific antitumor therapy is to become a useful treatment approach. [a] large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." It is clear from Jen et al that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome.

It is noted that the Galderisi et al (cited by applicant) reference describes some specific methodologies using specific antisense oligonucleotides that have undergone extensive characterization and experimentation before their use in the treatments described. It has been asserted that the reference provides evidence that general methodologies can be used in the treatment of any disease with antisense. It is noted that the Galderisi et al reference states "[t]he concept of antisense technology is simple.

However, the development as broadly applicable therapeutic agents has been slow and difficult." (page 251) and, "[t]he use of antisense molecules to modify gene expression is variable in its efficacy and reliability, raising objections about their use as therapeutic agents." (abstract) { these two statement indicate that, although there has been some success, results are not predictable}, and, [w]hile the mechanism involved in cellular ODN uptake still is not clear, there is also great variation between different cell types with regard to their ability to internalize oligo molecules." (page 252) {has the instant specification taught a predictable method of delivering sufficient amounts of oligonucleotide to cells such that dementia will be treated or prevented?}, and assert at page 253 that the observed effects in the example of success that "these compounds may have some therapeutic efficacy likely through a combination of antisense and non-sequence dependent effects on gene function." Galderisi et al conclude with the assertion that "[t]he use of antisense to modify gene expression is variable in both efficacy and reliability, which caused objections about its use as a therapeutic agent. Most of these concerns can be overcome by the development of a new generation of antisense molecules with improved target specificity and enhanced delivery to the target cells." It does not appear that the instant application discloses a new generation of antisense oligonucleotides that overcome the unpredictability of the art and that general methodologies are insufficient in the use of antisense to treat any particular disease, for example. In view of that argued above and in view of the large volume of experimentation apparently needed to perform the claimed treatment or prevention of dementia via antisense it would appear to reach the level of undue experimentation

since the specification only provided general guidance. Furthermore, the type of experimentation required to practice the invention more broadly than exemplified is a factor in the enablement analysis, but it not dispositive. In this case, the more or less standard nature of each type of experimentation required to expand the scope of an enabled invention is outweighed by the sheer quantity of experimentation to practice the full scope of the claims, the unpredictability of the art generally and the claimed method in particular, and the lack of guidance in the specification regarding the direction in which the experimentation should proceed.

One in the art would be required to engage in undue trial and error experimentation to practice the claimed invention since the specification as filed has failed to provide any particular sequences of the various antisense based compounds recited in the claim that would predictably be effective an effectively delivered to target cells in the treatment or prevention of dementias of Alzheimer's type of neuronal degeneration and also fails to provide with any particularity how one would specifically treat or prevent dementias of Alzheimer's type of neuronal degeneration with antisense based nucleic acid compounds.

(10) Response to Argument

Appellants argue that the scope of the present claims is commensurate in scope with the teachings of the specification and the prior art. It is the examiners position that the scope of what is claimed is outside the scope of what is taught in the specification

and the knowledge of one skilled in the art. Appellants argue that the scope of the invention is not broad since the claims are limited to the treatment of an animal in need of treatment of dementias of the Alzheimer's type of neuronal degeneration and also specifies the characteristics of the oligonucleotides. It is noted that even to such a limited target one in the art would be required to de novo/empirically screen thousands of potential antisense oligonucleotides.

Appellant asserts that the art of antisense-based therapy was well established at the time of invention. It is noted that the specification cites several methods of providing antisense to cells and to organisms. None of these methods has been shown in the art to be a routine and predictable means of delivery for all antisense application (e.g. for treating any particular disease). Appellant notes that there are successful applications of antisense noted in the art. This has not been disputed, but it is not agreed that these successes are demonstrative of a well-established and predictable art. Appellant cites Galderisi et al and Agrawal et al to show success. It is noted that these examples have been treated in the rejection of record. It is noted also that the Agrawal examples are directed to models and do not show the success in the treatment of a disease *per se*. Both of the references discuss the successes in the art and both still indicate that much needs to be developed to make the application of antisense therapy predictable. Appellant also asserts that Galderisi provides a discussion of Vitravene™ as an example that the art is well established. The antisense oligonucleotide of Vitravene™ is administered intravitrally and does not have the problems associated with delivery as asserted in the rejection of record.

Appellant asserts that the use of antisense for therapeutic purposes is predictable. Appellant asserts that although various considerations are taken into account in selecting an antisense sequence and deciding upon an appropriate method of cellular delivery, the specification provides substantial guidance regarding these aspects. It is the examiners position the specification provides general options of where one might start without any specific guidance on how to treat a specific disease with a predictable delivery means with an antisense oligonucleotide that would predictably function in its targeted environment. Furthermore the art relied upon in the rejection clearly demonstrates that one in the art would not predict that any particular mode of delivery would routinely function in any of a variety of applications (e.g. various diseases that manifest in various tissue and/or cell types). Applicant argues that target sequence selection would have been highly predictable in view of the claim language and the teachings in the specification. It is noted that the rejection of record addresses this argument by showing that even though the type of experimentation required to practice the invention more broadly than exemplified is a factor in the enablement analysis, it not dispositive. In this case, the more or less standard (albeit empirical and unpredictable) nature of screening for an active antisense in cells and the nonroutine experimentation required to find a means of providing a sufficient amount of an antisense that will be effective in an animal antisense to a target tissue and/or cell for sufficient time to treat a condition required to expand the scope of an enabled invention is outweighed by the sheer quantity of experimentation to practice the full scope of the claims, the unpredictability of the art generally and the claimed method in particular, and the lack of

guidance in the specification regarding the direction in which the experimentation should proceed. The use of the specific oligonucleotides SEQ ID NO: 9, 10, and 11, do not rectify the lack of guidance for delivery, for example.

Appellant also argues that cellular delivery of antisense oligonucleotides was predictable at the time of filing. Delivery to cells in culture was indeed more predictable than delivery to an animal as is made clear from the references and the rejection of record. The claimed invention is drawn to delivery to an animal not cells in culture.

Appellant asserts that the examiner has failed to establish that the art of antisense therapeutics is unpredictable. Appellant argues that the Agrawal reference deals with the unpredictability of antisense in cells in culture, but it is noted that the instant specification fails to provide even cellular data, for example. Applicant asserts that the Branch reference teaches that non-antisense effects might be advantageous, however, there has been no disclosure of or discussion of non-antisense in the instantly claimed invention being an advantage that overcomes the unpredictability of the art, for example. Applicant essentially argues, in the treatment of the cited references, that routine experimentation is all that would be needed. Appellant cites the specification at page 31 lines 3-9 to show that the specification provides guidance for delivery. It is noted that the text is general and requires one in the art to make determination where thereis no specific guidance for the treatment of any particular disease, for example.

In a nut shell, the prior art cited by the examiner and that cited by appellant shows that screening for antisense that function in cells is empirical and that once an antisense is found to be effective in cells in culture it is not then predictable that it will

function in an *in vivo* setting and then on top of that the prior art teaches that experimentation needs to be done to find means to effectively deliver antisense in vivo before antisense therapy is routine. The instant specification does not provide sufficient guidance such that one of skill in the art would be able to practice the claimed invention without performing undue experimentation to overcome the above. It is interesting to note that in the same references that applicant cites as providing evidence by pointing to studies in animal models also indicate that much work needs to be done in order for antisense therapeutics to be realized.

Appellant asserts that

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Sean McGarry

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